DISCUSSION PAPER

Breast Cancer Management in the TAILORx Era: Less is More

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Introduction

Breast cancer is the most common malignancy among women in the United States, with over 260,000 new cases and over 40,000 deaths estimated to occur in 2018 [1]. Although most breast cancers are diagnosed with disease localized to the breast or breast and regional lymph nodes, and thus amenable to surgery, the development of metastases to distant organs is the primary cause of death. Breast cancer deaths have been decreasing, in part due to the use of adjuvant systemic therapies, including chemotherapy, endocrine therapy, and anti-HER2-targeted therapy, which decrease metastatic recurrence [2]. The decision to treat patients with adjuvant therapy is guided by prognostic factors, such as tumor size, grade, and involvement of axillary lymph nodes, and predictive factors, such as expression of hormone receptors (HR) and HER2, which are predictive of benefit from adjuvant endocrine therapy (ET) and anti-HER2 therapy, respectively.

Diagnostic tests that measure expression of multiple genes (multiparameter gene expression assays) provide prognostic information that is complementary to classical clinicopathologic features such as tumor size and grade, and some also provide predictive information regarding benefit of adjuvant therapies. These tests measure the RNA expression level of multiple genes, and combine this information into a signature to help determine the prognosis of patients diagnosed with breast cancer. Several such multiparameter tests have been developed and approved for use in the United States, but the 21-gene Oncotype DX assay (Genomic Health, Redwood City, CA) is associated with the most robust data regarding prediction of benefit from cytotoxic chemotherapy for early hormone receptor positive (HR+) breast cancer [3,4,5]. The recently published data from the Trial Assigning Individualized Options for Treatment (TAILORx) study, has demonstrated that the majority of women with HR+, HER2-negative, node-negative breast cancer derive no benefit from adjuvant chemotherapy [4]. This paper reviews the TAILORx trial and its implications for treatment of women with early breast cancer.

Rationale for Adjuvant Chemotherapy in Early HR+ Breast Cancer

Multiple randomized trials performed in the 1980's and 1990's demonstrated that adjuvant chemotherapy decreased risk of recurrence in patients with early breast cancer [6,7] and that chemotherapy provided additional benefit beyond ET alone for women with HR+ disease [8,9]. For example, the NSABP B20 trial, which randomized over 2,300 women with estrogen receptor-positive (ER+) node-negative breast cancer to tamoxifen alone or in combination with 6 cycles of adjuvant chemotherapy, demonstrated that addition of cytotoxic chemotherapy significantly reduced the risk of recurrence (HR=0.52; $p<0.0001$) and death (HR=0.78; $P=0.063$) over 12 years of follow-up [8]. Subsequent meta-analyses, coordinated by the Early Breast Cancer Trialists Collaborative Group, demonstrated that the proportional reduction in risk of recurrence from adjuvant chemotherapy is only minimally affected by clinicopathologic factors such as tumor size, tumor grade, nodal involvement, ER level, age, and use of ET [10,11]. Based on this data, the National Institutes of Health issued a consensus statement in 2000, advising that adjuvant chemotherapy be recommended to the majority of women with breast cancer, regardless of nodal, menopausal, or hormone-receptor status [12].

However, this strategy assumes that all patients derive the same potential benefit from adjuvant chemotherapy, resulting in overtreatment of a large number of women to benefit a few. While women with low-risk disease derive an equal proportional benefit from ad-

juvant chemotherapy to those at higher risk, they have a smaller absolute benefit, due to their lower baseline risk of recurrence. These women predominantly have early ER+, HER2 negative disease, and receive significant benefit from adjuvant ET [8]. In the early 2000's, several web-based tools (Adjuvant! Online, NHS PREDICT) were developed to estimate prognosis and chemotherapy benefit based on standard clinicopathologic variables, and to help oncologists and their patients make informed treatment decisions. However, prior to the advent of multiparameter gene expression assays, no reliable methods were available to predict which individual patient would benefit most from cytotoxic chemotherapy, and who could safely avoid it.

Development and Validation of the Oncotype DX 21-Gene Assay

The Oncotype DX breast cancer test evaluates expression of 21 genes (16 tumor-related genes and 5 reference genes) by rtPCR and calculates a recurrence score (RS) from 0-100, with higher scores indicating greater likelihood of recurrence (see *Figure 1*).

The prognostic utility of the Oncotype DX breast cancer test was prospectively validated using archival tumor specimens from 668 patients treated with tamoxifen who had been enrolled on the NSABP B14 clinical trial (which had studied the role of tamoxifen in node-negative ER+ breast cancer, and had shown that use of tamoxifen led to significant declines in risk of recurrence and death [8]). Using prespecified cutpoints for RS risk groups, 10-year distant recurrence (DR) rates were 6.8 % (95% CI 4.0-9.6) for a low RS (<18), 14% (8.3-20.3) for an intermediate RS (18-30) and 30.5% (23.6-37.4) for a high RS (>31) [13]. Subsequent prospective validation studies using archival tumor tissue samples showed that the assay was also prognostic for recurrence in women receiving aromatase inhibitors [14] and in women receiving chemotherapy in combination with endocrine therapy (chemoendocrine therapy, or CET) [15]

Two additional validation studies using archival tumor specimens demonstrated that, in addition to being prognostic for recurrence, the Oncotype DX test was also predictive of benefit from adjuvant chemotherapy. The first trial utilized tumor specimens from the NSABP B20 trial, which had demonstrated that cytotoxic chemotherapy provided additional benefit to tamoxifen in patients with node negative ER+ breast

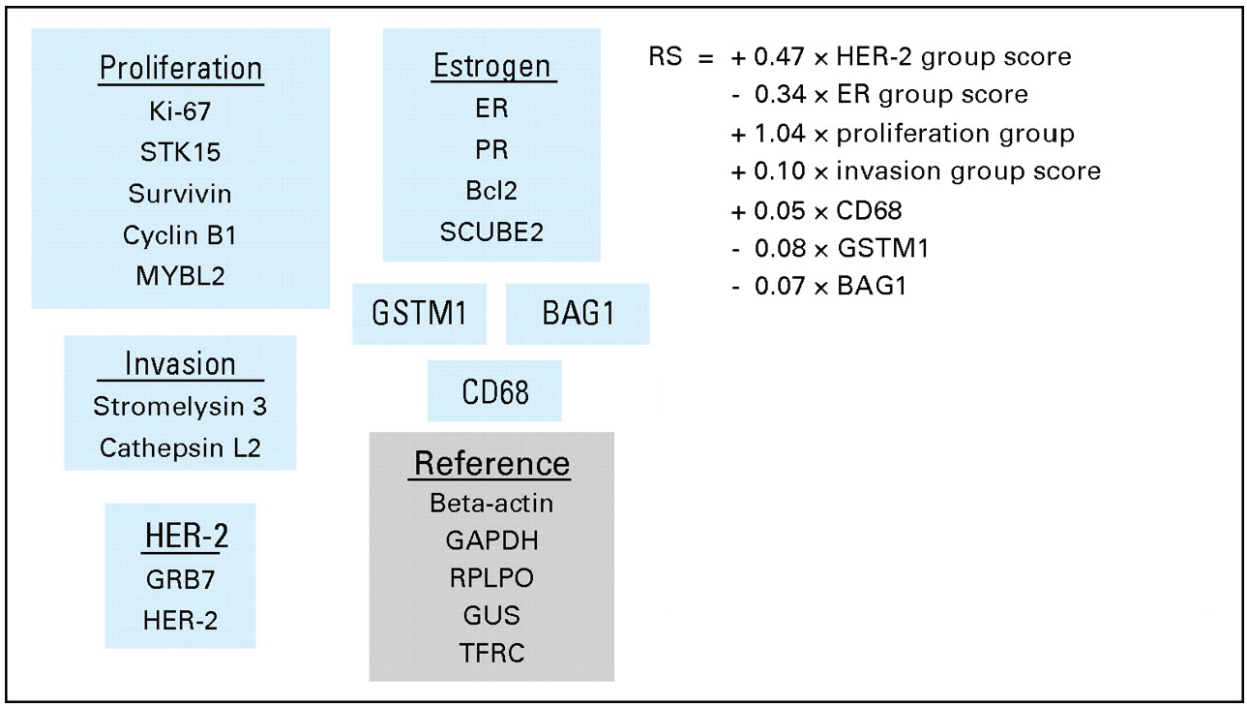

Figure 1 | Oncotype DX Recurrence Score (RS) Genes and Algorithm
SOURCE: Adapted from Sparano, J. and S. Paik, Development of the 21-Gene Assay and Its Application in Clinical Practice and Clinical Trials, *Journal of Clinical Oncology,* 26:721-728, 2008.
Note: ER - Estrogen receptor; PR – Progesterone Receptor

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cancer [8]. The validation trial demonstrated that women with RS<18 derived minimal to no benefit from chemotherapy. In contrast, women with RS>31 who received chemotherapy had an approximately 75% reduction in the relative risk of DR at 10 years, with an absolute decrease in DR of 27.6% (SE, 8.0%) at 10 years. However, the results were inconclusive regarding the benefit of chemotherapy for women with intermediate RS [3]. A second validation study, utilizing specimens from a subset of patients with node-positive, ER+ breast cancer treated with CET vs tamoxifen alone on the SWOG-8814 clinical trial, also demonstrated that chemotherapy predominantly benefited women with RS>31 [16].

Early Experiences with the Oncotype DX 21-Gene Assay in Clinical Practice

The Oncotype DX test became commercially available in 2004. In 2007, its use was endorsed by the American Society of Clinical Oncology (ASCO) expert panel on the use of tumor markers in breast cancer, which concluded that it had demonstrated clinical utility for prognostication of recurrence risk and prediction of chemotherapy benefit for newly diagnosed patients with node-negative, ER+ breast cancer treated with tamoxifen [17]. In 2009, guidelines issued by the National Comprehensive Cancer Network (NCCN) recommended consideration of Oncotype DX testing for women with ER+, HER2-negative, node-negative breast cancer, and potentially withholding chemotherapy for RS<18. [18].

Several early studies evaluating the impact of the Oncotype DX test on breast cancer treatment selection by physicians demonstrated changes in treatment recommendations for 20%-44% of patients undergoing testing, predominantly in the direction of recommending against chemotherapy based on low RS, and less often selecting for chemotherapy based on high RS [19,20,21,22]. Physician confidence in their treatment recommendations improved, and patient anxiety and decisional conflict declined, after receipt of Oncotype DX results [22]. However, these studies were not designed to evaluate patient benefit with respect to breast cancer outcomes as a result of testing.

Studies evaluating use of Oncotype DX in breast cancer clinical practice also found a relatively lower proportion of patients with high RS (> 31) [19,20,21,22] than had been seen in the validation trials [3,13,15,16], indicating that clinicians were selectively ordering the test for patients they believed to be at low or intermediate risk of recurrence, and reflecting exclusive use of the test in patients with HER2-negative disease (because HER2-positive disease is almost always associated with a high RS). Early post-marketing experience with the Oncotype DX test also revealed a lower than expected proportion of patients with high RS (15% of the first 20,500 tests ordered, vs 24-28% in the validation studies) [23], again demonstrating selection bias among physicians ordering the test.

Design of the TAILORx Trial

In order to prospectively evaluate the clinical utility of the Oncotype DX 21-gene assay, and evaluate the benefit of adjuvant chemotherapy for women with intermediate RS, the National Cancer Institute sponsored the TAILORx trial. In this trial, over 10,000 women with ER+, node negative breast cancer were prospectively assigned to postoperative treatment based on their RS. As the Oncotype DX validation studies had demonstrated minimal to no benefit for adjuvant chemotherapy in women with low RS, and clear benefit to chemotherapy in women with high RS, the TAILORx study assigned these patients to adjuvant ET alone and adjuvant CET, respectively. Women with intermediate RS were randomized to CET vs ET alone.

The RS ranges for low (RS<10), intermediate (RS 11-25), and high risk (RS>26) disease utilized in the TAILORx trial were different from those originally defined by the validation studies (low risk <18, intermediate 18-30, high risk <31). The rationale for this change was 3-fold: (1) to account for the absence of patients with HER2+ breast cancer in the TAILORx study population, because the Oncotype DX test includes a HER2 module, and most HER2+ tumors have a high RS, (2) to better emulate the way that the test was used in clinical practice, and (3) to minimize the potential for undertreatment in patients randomized or assigned to ET alone. A re-analysis of the NSABP B20 validation data using the adjusted RS cutpoints showed preservation of chemotherapy benefit in the high risk group, and recurrence risk of 5% or less with tamoxifen alone in the low and intermediate risk groups [23]. A subsequent analysis demonstrated similar prediction of chemotherapy benefit using a RS of 26 or higher when those with HER2+ disease were excluded [24].

The TAILORx trial enrolled women with HR+, HER2-negative, node-negative breast cancer who had undergone surgery, met national guidelines for recommendation or consideration of adjuvant chemotherapy (age 18-75, tumor size 1.1 to 5 cm, or 0.6-1 cm if in-

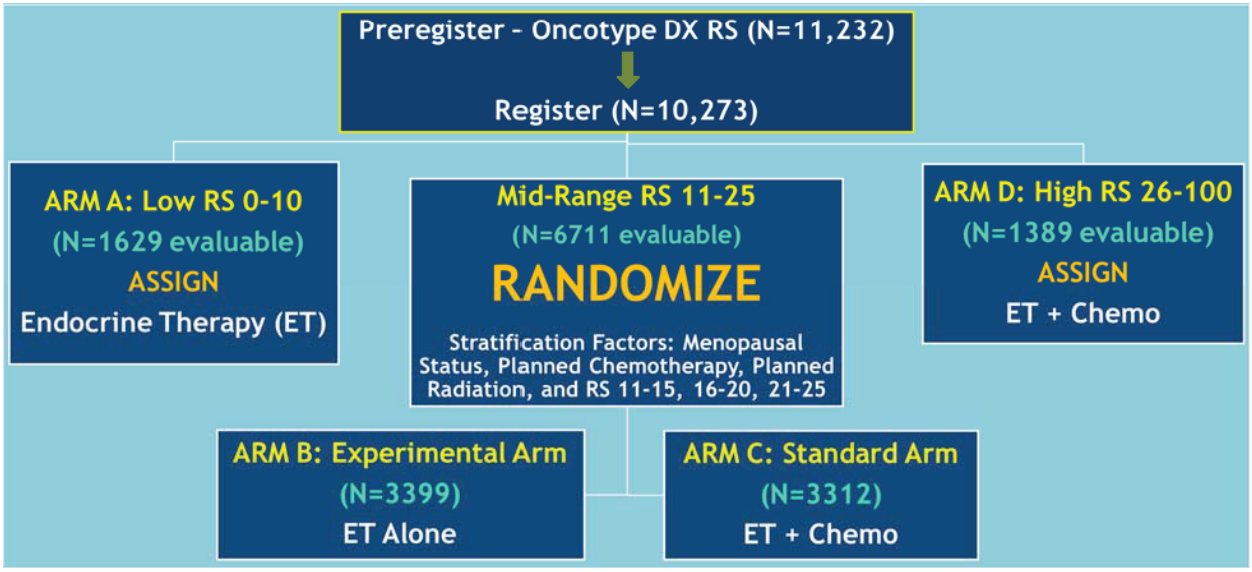

Figure 2 | Design of the TAILORx Trial
SOURCE: Reprinted with permission from Sparano, J. A. et al, *Trial Assigning Individualized Options for Treatment (TAILORx): Phase III trial of chemoendocrine therapy vs. endocrine therapy alone in hormone receptor-positive, HER2-negative, node negative breast cancer and an intermediate prognosis 21-gene recurrence score.* Presented at the ASCO Annual Meeting 2018.

termediate to high grade, and no other medical conditions that would preclude chemotherapy), had tumor tissue available for Oncotype DX testing, and were willing to have their treatment assigned or randomized based on RS.

The schema for the TAILORx trial is shown in *Figure 2.* 11,232 women were preregistered, and had their tumor specimen sent for the 21-gene Oncotype DX test. Of these, 10,273 women were registered and had treatment assigned or randomized based on their RS result, and 9719 were included in the main analysis. 1629 (17%) women with RS 0-10 were assigned to ET alone, 1389 (14%) with RS>26 were assigned to CET, and 6711 (69%) women with RS 11-25 were randomized to receive either CET vs ET [4,5].

Results of the TAILORx Trial

Results from the low-risk patient cohort were published in 2015, and demonstrated 5-year rates of invasive disease-free survival (DFS), distant relapse-free interval (DRFI), and overall survival (OS) of 94% (SE 0.6), 99.3% (SE 0.2) and 98% (SE 0.4) respectively, prospectively confirming the excellent prognosis for women with HR+ node-negative breast cancer and low RS in the absence of chemotherapy [5].

Results from the randomized patient cohort were published in 2018, and demonstrated that ET alone was non-inferior to CET for invasive DFS (HR 1.08, 95% CI 0.94, 1.24, p=0.26) in women with RS 11-25 in the intention-to-treat (ITT) population, the primary study endpoint. At 9 years, the estimated event rates for patients randomized to receive ET or CET were 83.3% versus 84.3% respectively for invasive DFS, 94.5% versus 95.0% for freedom from recurrence of breast cancer at a distant site, 92.2% versus 92.9% for freedom from recurrence of breast cancer at a distant or local-regional site, and 93.9% vs. 93.8% for overall survival. Although non-compliance rates with assigned therapy in the randomized arms was 12%, ET was likewise non-inferior to chemotherapy for DFS and freedom from distant recurrence for the as-treated population (actual treatment received) and per-protocol population (excluding patients who did not receive assigned therapy). Subgroup analysis for the ITT population showed significant interactions between chemotherapy effect, age, and RS, such that women under age 50 with RS 16-25 exhibited a small benefit from chemotherapy. Chemotherapy administration in these women led to a decrease in DR at 5 and 9 years by 0.8% and 1.6% respectively for RS 16-20, and 3.2% and 6.5% respectively for RS 21 to 25, although overall survival was not improved during the follow-up period [4].

The TAILORx trial demonstrated that approximately 70% of women with HR+ HER2-negative node-negative breast cancer can safely avoid chemotherapy, including all women with RS 0-15, and women above age 50

with RS 0-25[4]. Women age <50 with RS 16-25, representing 14% of the study population, exhibited a small but statistically significant improvement in DFS with chemotherapy, likely partially associated with chemotherapy-induced ovarian suppression [4]. Reduction in DR rates differed by RS in this population of younger women, with a 2% reduction observed for a RS 16-20, and 7% for a RS 21-25.

Other Trials Evaluating the Oncotype DX 21-Gene Assay

PlanB

The German PlanB trial was a prospective randomized study of two different chemotherapy regimens in 3198 patients with node-positive or high-risk node negative (defined as tumor size >2 cm, intermediate or high grade, ER-negative, or patient age <35), HER2 negative breast cancer. Women with ER+ disease involving 0-3 axillary nodes and RS<11 were recommended to omit chemotherapy. 5 year DFS for these patients (n=348; 238 node-negative, 110 node-positive) was 94.2% (95% CI, 91.2-97.3%), and was similar for women with node negative disease, and for those with up to 3 involved axillary nodes (94.2% [95% CI, 90.4=98-0%] and 94.4% [95% CI, 89.5-99.3%], respectively. [25,26].

Population-Based Evaluations

As use of gene expression tests to guide selection of breast cancer therapy became widely adopted in clinical practice, several population-based studies were able to evaluate the impact of RS on breast cancer outcomes. These studies demonstrate similar outcomes to those seen in TAILORx. Petkov, et al. utilized data from the Surveillance, Epidemiology, and End Results program to study 45,287 patients with HR+ non-metastatic breast cancer and available RS results in the United States, demonstrating a 5 year breast cancer specific mortality (BCSM) of 0.4% (95% CI, 0.3–0.6%) for patients with node-negative, HER2-negative breast cancer and low-risk RS (>18), only 7% of whom received chemotherapy, and 1.0% (95% CI, 0.5–2.0%) for patients with up to 3 involved axillary nodes, 23% of whom received chemotherapy. BCSM increased with increasing RS, and RS was prognostic for BCSM in multivariable analysis (P<0.001) [27].

Stemmer et al evaluated breast cancer outcomes in a prospective registry study in Israel including women with ER+, HER2 negative breast cancer who were node negative (1801) [28] or had up to 3 involved axillary nodes (709) [29]. They also found that RS was prognostic for 5-year DR rate and breast cancer mortality. In the node-negative group, 5 year DR rate was 0.8% (95% CI, 0.4-1.7%) for 880 patients with low RS (<18), only 1.4% of whom received chemotherapy, 3.0% (95% CI, 2-4.5%) for 733 patients with RS 18-30, 23.7% of whom received chemotherapy, and 8.6% (95% CI, 5.4-13.7%) for 188 patients with RS>31, 87.2% of whom received chemotherapy [28].

Implications of the TAILORx Trial

The TAILORx results provide the highest level evidence supporting the clinical utility of the Oncotype DX 21 gene test to guide use of adjuvant chemotherapy for early breast cancer with an unprecedented level of precision. The most significant impact will likely be seen in the treatment of women with a mid-range RS of 11-25, who represented approximately two-thirds of the study population. While use of adjuvant chemotherapy for early breast cancer has declined substantially in the years between the design and publication of TAILORx [30], this decline was most pronounced for patients with low RS. Recent studies evaluating adjuvant chemotherapy use after gene expression testing with the Oncotype DX test indicate receipt of chemotherapy in up to 55% of node-negative patients with intermediate RS (defined as 18-30) [27,31,32], with increasing likelihood of receiving chemotherapy associated with numerical increase in RS [31,32], reflecting the clinical uncertainty that had been associated with an intermediate risk RS. Now that TAILORx has clarified the role of chemotherapy for these patients, use of adjuvant chemotherapy for patients with early breast cancer may decline further. Population-based data, as well as data from Genomic Health, indicate that the TAILORx study participants and their RS distribution were similar to those seen in clinical practice, demonstrating the generalizability of these findings to routine clinical care. Evaluation of the impact of the Oncotype DX test on breast cancer outcomes in large population-based cohorts has demonstrated similar findings to TAILORx [27,28]. Results from the PlanB trial suggest that women with a low RS and low-volume node-positive disease may also be spared chemotherapy [26].

The TAILORx trial provides robust prospective data on the use of a multiparameter gene expression test to guide therapy selection. Several gene expression assays have demonstrated clinical utility for determination of breast cancer prognosis, and are approved for use in the United States. However, these tests have not been shown to predict benefit from adjuvant chemotherapy. In addition, direct comparison of several gene expression tests (including Oncotype DX) have shown

substantial variation in risk stratification among tests [33,34], suggesting that the TAILORx data should not be extrapolated to other assays. A prospective study utilizing the 50-gene Prosigna test to guide administration of adjuvant chemotherapy in early breast cancer is currently in progress [35].

To date, the only other published prospective randomized trial of therapy selection for breast cancer guided by a gene expression test is the MINDACT (Microarray In Node-negative Disease may Avoid ChemoTherapy) trial, which evaluated the 70-gene MammaPrint assay in a heterogeneous group of 6693 patients with early breast cancer (hormone receptor and/or HER2 positive or negative, with up to 3 involved axillary nodes). All patients underwent MammaPrint testing and assessment of clinical risk by the Adjuvant!Online algorithm, which defined low clinical risk as 10-year likelihood of breast cancer specific survival without systemic therapy above 88% for ER+ disease (corresponding to 92% with adjuvant endocrine therapy) and above 92% for ER-negative disease. Women whose tumors were considered high risk by both MammaPrint and clinicopathologic features (n=1806; 27.0%) were advised to receive chemotherapy; women with concordant low risk disease (n=2745; 41.0%) were advised against chemotherapy; and women with discordant results (that is, those with low clinical risk and high genomic risk [592 (8.8%)], or with high clinical risk and low genomic risk [1550 (23.2%)]) were randomized to treatment based on genomic risk or based on clinical risk. The MINDACT trial met its primary endpoint, which was to assess whether a subgroup of 644 patients who were clinically high risk and genomically low risk, and who were randomized to not receive chemotherapy, had a 5-year distant metastasis-free survival (DMFS) of at least 92% [36]. The authors therefore concluded that these patients might be able to avoid chemotherapy. However, although the MINDACT trial was not designed or adequately powered to evaluate whether the MammaPrint test was predictive of chemotherapy benefit, there was some evidence of chemotherapy benefit among those with a low-risk 70 gene profile and high clinical risk. In the entire group of 1228 patients with high clinical risk and low genomic risk, there was improved 5-year DFS (93.3% vs. 90.3%, hazard ratio 0.64, p=0.03), and trend toward improved survival without distant metastasis (96.7% vs. 94.8%, hazard ratio 0.65, p=0.11) among those assigned to treatment by clinical risk (with CET) compared with those assigned to treatment by genomic risk (with ET alone) [36]. Conversely, among the 478 patients with low clinical risk and high genomic risk, treatment by genomic risk (with CET) was not associated with significant benefit compared to treatment by clinical risk (ET alone), indicating that prediction of chemotherapy benefit in patients with low clinical risk but high genomic risk could not be established. Taken together, these results indicate that although low-risk 70-gene profile was prognostic, it was not predictive of chemotherapy benefit. Evidence-based guidelines state that the 70-gene MammaPrint test may be considered for patients with hormone-receptor-positive, HER2-negative breast cancer and high clinical risk, but not for patients with low clinical risk as defined by the MINDACT study [37].

As of this writing, several of the most recently updated national guidelines for breast cancer management were developed after publication of the data from the TAILORx low risk patient cohort that confirmed excellent prognosis of women with RS 0-10 in the absence of chemotherapy [5], but prior to publication of the results for the randomized cohort with intermediate RS. The 2016 ASCO guidelines for use of biomarkers in breast cancer incudes the Oncotype DX test as one of several which may be used to guide treatment decisions for patients with HR+, HER2-negative, node negative breast cancer [38]. Oncotype DX results were also incorporated into the 8th edition of the American Joint Committee on Cancer (AJCC) Staging System, which took effect in January 2018. Under this staging system, breast cancers are staged using a combination of anatomic extent of disease and prognostic markers for recurrence. Thus, tumors bearing markers associated with favorable prognoses are down-staged, while those with poorer prognostic markers are up-staged. Under this system, any ER+ HER2-negative node-negative breast cancer under 5 cm with RS<11 is down-staged to a Prognostic Stage Group of IA. The AJCC Breast Cancer Expert Panel did not conclude that any other multiparameter gene expression test had generated robust enough data to alter tumor stage [39].

The NCCN guidelines, in contrast, were amended in October 2018 to incorporate the TAILORx data from the randomized patient cohort. The new guidelines strongly endorse utilization of the Oncotype DX 21-gene assay to guide treatment decisions for node negative, ER+, HER2 negative breast cancer, and incorporate the adjusted cutpoints for low, intermediate, and high risk RS into their management algorithm. The new guidelines state that Oncotype DX is the preferred multigene test for guiding treatment decisions in this patient population, as other multigene assays have not been validated to predict chemotherapy benefit [40,41].

The TAILORx findings raise the question of whether the results can be extrapolated to women with more regionally advanced breast cancer with positive axillary lymph nodes. Population-based data [27, 29], and the prospective PlanB trial [25], support the use of the Oncotype DX to spare women with RS<11 and low volume axillary nodal involvement from treatment with chemotherapy. The most recent NCCN guidelines state that use of gene expression tests may be considered to determine prognosis in patients with ER+, HER2- negative breast cancer, and 1-3 involved axillary lymph nodes who are candidates for chemotherapy [41]. This question is being addressed prospectively in the ongoing RxPONDER trial, in which women with ER+ HER2- negative breast cancer with involvement of 1-3 axillary nodes and RS< 25 are randomized to CET vs ET alone [42]. This study has completed accrual, but results are not yet available.

Conclusions

Multiparameter gene expression tests provide prognostic information that is complementary to classical clinicopathologic features like tumor size and grade in early stage breast cancer. The Oncotype DX 21-gene assay is associated with the most robust data regarding prediction of chemotherapy benefit in patients with early HR-positive, HER2-negative breast cancer, allowing greater precision in guiding the use of adjuvant chemotherapy. The results of the prospective RxPONDER clinical trial, when available, will provide more information about use of this test to potentially spare women with up to 3 positive axillary nodes from undergoing chemotherapy.

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